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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/615,571	07/13/2000	Paul Harris	5951.010.US	4949

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EXAMINER	
PRIEBE, SCOTT DAVID	

ART UNIT	PAPER NUMBER
1632	8

DATE MAILED: 12/07/2001

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/615,571	HARRIS ET AL.	
	Examiner	Art Unit	
	Scott Priebe	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 September 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *71-99* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *96-99* is/are allowed.

6)☒ Claim(s) *71-75,78-82 and 84-95* is/are rejected.

7)☒ Claim(s) *76,77 and 83* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *3* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

The Group and/or Art Unit designation of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Primary Examiner Scott D. Priebe, Ph.D., Group Art Unit 1632.

The amendment filed 9/20/01 has been entered. Claims 51-70 have been cancelled. Claims 71-99 have been added.

Information Disclosure Statement

The information disclosure statement filed 7/13/00 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each U.S. and foreign patent; each publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. It has been placed in the application file, but the information referred to therein has not been considered, except for the Masuda et al. reference, which was made of record by the Examiner in the parent application. Contrary to applicant's assertion, no information disclosure statement was filed in the parent application, and none of the other references were made of record by the Examiner; see the face of US 6,146,869. Applicant is advised that should they desire that other references be considered, they must file a new information disclosure statement that meets the requirements of 37 CFR 1.97 and 1.98, including the fee if filed in response to this Office action..

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 78 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 78 is directed to a nucleic acid sequence that encodes a phospholipase B consisting of amino acids 20 to 264 of SEQ ID NO: 2. The specification as originally filed does not disclose this fragment of SEQ ID NO: 2, nor that this fragment has phospholipase activity. This subject matter was added in the preliminary filed with the application. However, the original declaration does not refer to this preliminary amendment as being part of the original disclosure. See MPEP 608.04(b). It appears that recitation of "264" is a typographical error, and should be --464--.

Claims 71-75, 79-82, 84-87, and 91-95 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 71-75, 79-82, and 84-95 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a nucleic acid sequence encoding a phospholipase B wherein either the nucleic acid sequence comprises nucleotides 568 to 2045 of SEQ ID NO: 1 or the polypeptide comprises amino acids 20-464 of SEQ ID NO: 2 , does not reasonably provide enablement for any other embodiments lying outside this scope. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

While the written description and enablement requirements of 35 USC 112, 1st para. are separable, in this instance the facts and issues are so interrelated that the specification fails to meet both requirements for the genus of polynucleotide being claimed for essentially the same reasons. The specification does not adequately describe those structural, physical and chemical characteristics of the claimed nucleic acids or the phospholipase B they encode that distinguish them from nucleic acid sequences which are not claimed. Consequently, there is no evidence that Applicant had conception or possession of the generic nucleic acid sequences being claimed. As to enablement, one cannot make what one cannot conceive.

The claims are directed to nucleic acid sequences which encode a generic phospholipase B, with the claimed nucleic acid sequences further limited by a broad structural relationship between the amino acid sequence of the generic phospholipase B or the generic nucleotide sequence of the claimed nucleic acid sequence and a single species of amino acid sequence and nucleotide sequence, respectively, whose complete structures are disclosed in the specification.

Specifically, the claims are directed to: a) a nucleic acid sequence that encodes a phospholipase B is at least 80%, 90%, 95%, or 97% identical to amino acids 20-464 of SEQ ID NO: 2 or b) a nucleic acid sequence that is at least 80%, 90%, 95%, or 97% identical to nucleotides 568-2045 of SEQ ID NO: 1 and encodes a phospholipase B. The only genus described in the specification that clearly meet both the structural and functional limitations of (a) or (b) are a nucleic acid sequence encoding a polypeptide encoding amino acids 20-464 of SEQ ID NO: 2, which is the mature phospholipase B of *Aspergillus oryzae* BECh2. This adequately described genus would include a nucleic acid sequence that comprises nucleotides 568-2045 of SEQ ID NO: 1 and nucleic acid sequences that are 80% identical to nucleotides 568-2045 of SEQ ID NO: 1 that encode amino acids 20-464 of SEQ ID NO: 2. One skilled in the art can readily envision and determine, without experimentation, which nucleotide sequences would encode a particular amino acid sequence. Thus, conception of the generic nucleic acid sequence is largely controlled by the amino acid sequence of the phospholipase B encoded, rather than by its actual nucleotide sequence. However, the specification does not provide evidence that Applicant was in possession of a nucleic acid sequence that encodes a phospholipase B that is does not at least comprise amino acids 20-464 of SEQ ID NO: 2, for the reasons set forth below.

It is important to note that the claims are no way limited to nucleotide sequences that can be isolated from nature, nor to nucleotide sequences encoding a phospholipase B found in nature. Indeed, most of the operable embodiments embraced by the claims probably do not occur in nature.

The court and the Board have repeatedly held (*Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*,18 USPQ2d 1016 (CA FC, 1991); *Fiers v. Revel*, 25 USPQ2d 1601 (CA FC 1993); *Fiddes v. Baird*, 30 USPQ2d 1481 (BPAI 1993) and *Regents of the Univ. Calif. v. Eli Lilly & Co.*, 43 USPQ2d 1398 (CA FC, 1997)) that an adequate written description of a nucleic acid requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it, irrespective of the complexity or simplicity of the method; what is required is a description of the nucleic acid itself. It is not sufficient to define DNA solely by its principal biological property, because disclosure of no more than that, as in the instant case, is simply a wish to know the identity of any DNA with that biological property. Naming a type of material generically known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material. When one is unable to envision the detailed constitution of a complex chemical compound having a particular function, such as a nucleic acid, so as to distinguish it from other materials, as well as a method for obtaining it, conception has not been achieved until reduction to practice has occurred, i.e., until after the nucleic acid has been isolated. Thus, claiming all DNA's that achieve a result without defining what means will do so is not in compliance with the description requirement. Rather, it is an attempt to preempt the future before it has arrived. Also, where a claim purports to cover all nucleic acids that encode a specific protein and the specification discloses but a single DNA known to do so, the situation is analogous to a single means claim and does not meet the enablement requirement under para. 1 of §112. The court has also held that a claimed nucleic acid could meet the written description

and enablement requirements if the nucleic acid were defined by a disclosed process found, after-the-fact, to produce the nucleic acid, and claimed as a product-by-process. However, in the instant case, the nucleic acids are not claimed as a product-by-process, nor does the specification disclose any process known to yield a claimed nucleic acid.

The only difference between the cases reviewed by the court and Board, and the instant case, is that in addition to recitation of the desired protein activity, the claims also recite a broad arbitrary structural relationship between the claimed nucleic acid sequence, either in terms of its nucleotide sequence or the polypeptide encoded, and the single disclosed species of nucleotide sequence and amino acid sequence, respectively. Consequently, the claims do not purport to claim *all* nucleotide sequences which encode a particular functional protein. However, this distinction does not aid Applicant's cause here. The recited structural relationships are arbitrary since neither the specification nor the prior art discloses any definitive relationship between protein function and % identity or homology at either the nucleotide or amino acid level; and the specification does not describe a single species of nucleic acid that encodes a functional protein that is not either 100% identical to the recited nucleotide sequence or that encodes a polypeptide that is not 100% identical to the recited amino acid sequence.

While one of skill in the art can readily envision numerable species of nucleic acid sequences that are at least 80% identical to the recited reference nucleotide sequence and that encode a polypeptide that is at least 80% identical to the recited reference amino acid sequence, one cannot envision which of these also encode a polypeptide with phospholipase B activity. The

fact remains that the actual nucleic acid sequences which encode a protein with a particular activity or the actual amino acid sequences of such a protein *cannot* be envisioned any better when the possible choices are narrowed from all possible sequences to all possible sequences with an arbitrary structural relationship with a known functional sequence. For example, if one skilled in the art were to make a nucleotide sequence that encoded a polypeptide with 90% identity to the reference amino acid sequence, he would be no more able to say whether it encoded a phospholipase B than if the nucleotide sequence encoded a polypeptide that was only 10% identical to the reference polypeptide sequence.

To put the situation in perspective, the number of possible amino acid sequences of 100 amino acids in length is 20^{100} (approx. 10^{130}) and the number of possible nucleotide sequences of 300 nucleotides in length is 4^{300} (approx. 4×10^{180}) . The number of possible nucleotide or amino acid sequences that are of a given %identity relative to a reference sequence, where all differences between the possible sequences and the reference sequence are substitutions, can be calculated by the following formula:

$$N = XL + X^2L(L-1)/2! + X^3L(L-1)(L-2)/3! + ... + X^{n-1}L(L-1)(L-2)...(L-(n-2))/(n-1)! + X^nL(L-1)(L-2)...(L-(n-1))/n!$$

where N is the number of possible sequences, X is the number of different residues that can be substituted for a residue in the reference sequence, L is the length of the reference sequence, n is the maximum number of residues that can be inserted, deleted or substituted relative to the

reference sequence at a given % identity. For a nucleotide sequence, X is 3 (alternate nucleotides); for an amino acid sequence, X is 19 (alternate amino acids).

For a 100 amino acid sequence that is at least 90% identical to a reference sequence of 100 amino acids, the number of possible sequences having 9 amino acid substitutions relative to the reference (the penultimate term of the formula) is approximately 6×10^{23}. Whereas the number of possible sequences having 10 amino acid substitutions relative to the reference (the final term of the formula) is approximately 1.1×10^{26}. So the last term is approximately equal to N, i.e. the preceding terms contribute little to the total. It can also be shown that N can be approximated by the formula $X^nL^n/n!$, where $n<<L$. Using this formula to approximate N in this example gives a value of 1.7×10^{26}. For a 300 nucleotide reference sequence, the number of possible 300 nucleotide sequences that are at least 90% identical to the reference is approximately 1.6×10^{56}.

In the present case, the reference amino acid sequence, positions 20-464 of SEQ ID NO: 2, is 445 amino acids long, and the reference nucleotide sequence, positions 568-2045 is 1478 nucleotides long. The total number of possible 445 amino acid sequences is about 10^{578}; and the total number of possible 1478 nucleotide sequences is about 10^{889}. Using the approximation formula, the number of possible amino acid sequences and nucleotide sequences that are at least 80% identical to the reference amino acid sequence or nucleotide sequence, respectively, are approximately 10^{213} amino acid sequences and 10^{473} nucleotide sequences, respectively. While limiting the scope of potential sequences to those that are at least 80% identical to a reference

greatly reduces the number of potential sequences to test (from 10^{578} to 10^{213} amino acid sequences or from 10^{889} to 10^{473}), it does not do so in any meaningful way. All of these values greatly exceed the estimated number of atoms in the universe (10^{70} to 10^{90}). Thus, limiting the claims by the recited structural relationships merely reduces the degree of impossibility of making and testing sequences for those which encode a phospholipase B. Therefore, inclusion of the structural relationships in the claim does not distinguish the instant fact situation from those reviewed in *Amgen, Fiers,* and *Regents of the Univ. Calif.*

The specification at page 9, line 7 to page 10, line 5 discloses that the polypeptides of the invention (described originally by structural relationships of at least 65% identity or homology) may be obtained from bacteria and fungi and lists a number of species. The specification further suggests that the nucleic acid encoding these polypeptides could be cloned by a method including hybridization using fragments of SEQ ID NO: 1 as a probe. However, the specification does not disclose whether any of the bacteria or fungi listed on pages 9-10 other than *A. oryzae* have either a nucleic acid or phospholipase B that meets the limitations of the instant claims. For example, it does not disclose whether or not any of these species produce a phospholipase B that is at least 80% identical to amino acids 20-464 of SEQ ID NO: 2 or a nucleic acid encoding a phospholipase B that is at least 80% identical to nucleotides 568-2045 of SEQ ID NO: 1. All the specification does is provide a possible plan for obtaining other nucleic acid sequences embraced by the claims, the success of which is completely unclear.

The only prior art protein found by applicant to have any homology to the instant phospholipase B (EC 3.1.1.5), was a phospholipase C (EC 3.1.4.3)from *Pseudomonas aeruginosa*, with 26% identity. However, this prior art protein is not a phospholipase B, which hydrolyzes either fatty acyl bond of a phospholipid. Phospholipase C performs a different enzymatic reaction, hydrolyzing the glycerol phosphate ester bond. There is no evidence of record of any prior art phospholipase B that shares significant homology with the instant phospholipase B. A search of the protein databases by the PTO failed to reveal that *any* prior art phospholipase B, including that of Masuda et al. from *Penicillium notatum* and of Lee et al. from *Saccharomyces cerevisiae*, share significant homology with the instant phospholipase B. The only prior art proteins identified that had any significant homology with instant SEQ ID NO: 2 were phospholipases C or acid phosphatases from various bacteria and fungi. Löffler et al., US 5,965,422, discloses a phospholipase B (a.k.a. lysophospholipase) and a nucleic acid sequence encoding it, found in *Aspergillus foetidus*, SEQ ID NOs: 2 and 1, respectively. Comparison of the amino acid sequences of the phospholipase B from *Aspergillus foetidus* and the instant phospholipase B from *Aspergillus oryzae* does not reveal any significant homology (see attached sequence alignment). This shows that a particular protein activity can be possessed by proteins with very different and apparently non-homologous amino acid sequences; and that homologous proteins may have different activities. Furthermore, these results suggest is that Applicant's have discovered a new class of phospholipase B, with only a distant relationship to known phospholipases C and acid phosphatases, but not to known phospholipases B.

The specification does not provide any information on what amino acid residues are necessary and sufficient for phospholipase B activity. The specification also provides no teachings on what amino acid sequence modifications, e.g. insertions, deletions and substitutions, would be permissible in a phospholipase B polypeptide that would improve or at least would not interfere with the biological activity or structural features necessary for the biological activity and stability of the protein. Since there are no other examples of a phospholipase B known that have structural homology with SEQ ID NO: 2, it is not possible to even guess at the amino acid residues which are critical to its structure or function based on sequence conservation. Furthermore, it is known in the art that even conservative amino acid substitutions can adversely affect proper folding and biological activity if amino acids that are critical for such functions are substituted, and the relationship between the sequence of a polypeptide and its tertiary structure is neither well understood nor predictable (see Ngo, in The Protein Folding Problem and Tertiary Structure Prediction, Merz et al. (eds.), Birkhauser Boston: Boston, MA, pp. 433 and 492-495, 1994). Rudinger (in Peptide Hormones, Parsons (ed.), University Park Press: Baltimore, MD, pp. 1-7, 1976) discloses that even for peptide hormones, which are much smaller than the instant phospholipase B protein, one cannot predict variant amino acid sequences for a biologically active polypeptide. Rather one must engage in "case to case painstaking experimental study" to determine active variants (see page 7). Consequently, excessive trial and error experimentation would have been required to identify the necessary nucleic acid sequence derivatives encoding a

biologically active phospholipase B with an amino acid sequence differing from SEQ ID NO: 2 since the amino acid sequence of such polypeptides could not be predicted.

As set forth in *In re Fisher,* 166 USPQ 18 (CCPA 1970), compliance with 35 USC 112, first paragraph requires:

> that scope of claims must bear a reasonable correlation to scope of enablement provided by specification to persons of ordinary skill in the art; in cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific laws; in cases involving unpredictable factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with degree of unpredictability of factors involved.

In *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991), the court ruled that a claim to a large genus of possible genetic sequences encoding a protein with a particular function that needs to be determined subsequent to the construction of the genetic sequences may not find sufficient support under 35 USC 112, 1st para., if only a few of the sequences that meet the functional limitations of the claim are disclosed and if undue experimentation would be required of one skilled in the art for determining other genetic sequences embraced by the claim. This is the case here, where specification discloses only one functional amino acid sequences, SEQ ID NO: 2 amino acids 20 to 464, for a polypeptide having the necessary properties for the disclosed uses, and provides no guidance on obtaining polypeptide variants of SEQ ID NO: 2 which would be suitable.

With respect to claims 88-90, these claims do not require that the nucleic acid sequence encode a functional phospholipase B, nor that it be found in nature. The only disclosed use for this nucleic acid is to make phospholipase B or to detect a naturally occurring nucleic acid sequence encoding a phospholipase B. However, the specification does not disclose any such naturally occurring nucleic acid sequences other than SEQ ID NO: 1. The only method for making this nucleic acid sequence is to isolate it from an organism using hybridization under the recited conditions with a probe made from SEQ ID NO: 1 to detect clones. However, the specification does not disclose any organisms known to contain nucleic acid that would be detected by hybridization under the recited conditions. As discussed above, the disclosed nucleic acid appears to be a hitherto unknown class of phospholipase B gene. Furthermore. the claims as written would embrace any synthetic sequence that would hybridize to SEQ ID NO: 1 under the recited conditions. While a naturally occurring sequence might reasonably be expected to encode a phospholipase B, the vast majority of synthetic sequences clearly would not. For example, a nucleic acid sequence differing only by a single inserted or deleted nucleotide in the 5' end of the coding region would not encode any polypeptide resembling SEQ ID NO: 2, but it would hybridize to SEQ ID NO: 1 under the highest stringency conditions possible.

Also, the vast majority of claimed synthetic sequences would also be unusable as probes for naturally occurring nucleic acids encoding phospholipase B under the recited conditions. For example, a polynucleotide that is 80% identical to SEQ ID NO: 1, is likely to be much less than 80% identical, as low as 40% identical, to another nucleic acid molecule that is 80% identical to

SEQ ID NO: 1. Imagine a circle describing the genus of nucleic acid sequences at least 80% identical to SEQ ID NO: 1, with SEQ ID NO: 1 being at the center and those that are exactly 80% identical being on the circumference. Less than half of the nucleic acids that are at least 80% identical to one on the circumference would be inside the circle. Nucleic acid sequences on opposite sides of the circle would be only 40% identical, and those 90° apart would be only 60% identical. So, if a given organism should contain an unknown nucleic acid sequence that is at least 80% identical to SEQ ID NO: 1, one would not know which of the possible 10^{473} nucleic acid sequences would be a suitable probe under the recited conditions. If one were chosen randomly as a probe, it is more likely that it would be close to 40% identical to an unknown target sequence, which would not hybridize under the recited conditions, than close to 100% identical. The actual situation is much worse since the specification does not disclose which organisms such a nucleic acid sequence would be found. That would have to first be determined by using SEQ ID NO: 1 as probe, which would make unnecessary using any other probe that was less than 100% identical to SEQ ID NO: 1.

With respect to claim 87 which requires use of the deposited clone NRRL B-30142, this claim fails to meet the enablement requirement since the deposit made under the Budapest treaty does not meet all of the requirements under 37 CFR 1.801-1.809. Specifically it fails to meet the requirements of 37 CFR 1.808(a)(2), which requires assurance that the specific strain will be irrevocably and without restriction or condition released to the public upon the issuance of a patent. This requirement may be satisfied by an affidavit or declaration by applicants, or a

statement by an attorney of record over his or her signature and registration number, stating that the specific strain has been deposited under the Budapest Treaty and that the strain will be irrevocably and without restriction or condition released to the public upon the issuance of a patent, would satisfy the deposit requirement made herein.

Applicant's arguments filed 9/20/01 have been fully considered as they pertain to the new grounds of rejection set forth above but they are not persuasive. Much of the arguments are addressed in the rejection itself. The new claims narrow the scope of the claimed invention to polynucleotides that encode polypeptides that are 80% identical to SEQ ID NO: 2, amino acids 20-464; polynucleotides that are at least 80% identical to SEQ ID NO: 1, nucleotides 568-2045, or that hybridize to SEQ ID NO: 1, nucleotides 568-2045, under at least medium stringency conditions. The effect of these amendments only reduce the size of the genus which the specification did not adequately describe and did not enable. The primary issue here is whether the specification provides sufficient characteristics for the claimed invention to indicate that Applicant had possession of it and guidance on how to make it at the time the application was filed. As pointed out above referring to the pertinent case law, description of a potential method for making a product does not provide a description of the product itself; and none of the nucleic acid sequences are claimed as a product-by-process. Applicant's assertion that the disclosed method also enables how to make the claimed nucleic acids is self-serving, and Applicant has provided no evidence to support the assertion. The specification certainly does not, since no such nucleic acid other than SEQ ID NO: 1 is disclosed, and it was not isolated by the methods

Applicant refers to, i.e. involving hybridization to a probe from a nucleic acid encoding phospholipase B.

Whether one of skill in the art would be able to determine after-the fact using computer algorithms whether an particular sequence would be embraced by Applicant's claims is an issue under 35 USC 112, second paragraph, not first paragraph. In order to make such a determination, one would first have to possess the nucleic acid sequence. That Applicant even suggests one skilled in the art need make such a determination, demonstrates that Applicant was not in possession of the sequences in question. What Applicant is suggesting here is that one skilled in the art go out and clone phospholipase genes, sequence them, and then see if they meet the claim limitations. This is nothing more than a wish to know what the claim embraces, what nucleic acid sequences encode a phospholipase B.

Applicant asserts that *naturally* occurring nucleic acid sequences that are within 80% or 90% of SEQ ID NO: 1 or encode a polypeptide that are within 80% or 90% of SEQ ID NO: 2 are likely to encode phospholipase B; but provides no evidence for this. First and foremost, the claims are not limited to naturally occurring sequences. Most synthetic sequences would not encode a phospholipase B. Second, the specification does not disclose which organisms have nucleic acid sequences or polypeptides that are at least 80% identical to the reference sequences. Third, there are no prior art examples of phospholipase B that are homologous to the one disclosed, so the degree of sequence conservation among related genes and proteins is wholly unknown.

Applicant also asserts that is would be a simple matter for one skilled in the art to make "conservative amino acid substitutions that do not significantly affect the folding and/or activity of the protein". This assertion is unsupported. First and foremost, the specification does not teach which amino acid positions can tolerate even conservative substitutions without loss of function or structural integrity. Also, the prior art cited above contradicts this assertion. The ease with which one might "circumvent the literal scope of Applicant's patent right's" is not at issue, particularly since Applicant's patent rights have yet to be determined.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 80-82 and 88-90 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 80-82 each recite the limitation "nucleotides 568 to 2045 of SEQ ID NO: 2" in line 2. There is insufficient antecedent basis for this limitation in the claim. The term "SEQ ID NO: 2" should be replaced with --SEQ ID NO: 1--.

Claims 88-90 are incomplete and confusing. The claims are directed to a *nucleic acid sequence* isolated by hybridizing a *DNA* to a specified sequence, followed by isolating the *nucleic acid sequence*. It is unclear how hybridizing "a DNA" will allow isolation of a "nucleic

acid sequence", which are different entities. DNA is only one type of nucleic acid sequence, and the claim provides no nexus between the "nucleic acid sequence" (recited in the preamble and final step (b)) being isolated and the "DNA" used in hybridization. Finally, if the "DNA" is the "nucleic acid sequence", the claim is further unclear, since the claim as written would imply that the "DNA" is already isolated before it is hybridized. There is also a disconnect between steps (a) and (b). Step (b) merely recites what is isolated, but fails to indicate how the isolation relates to the hybridizing step.

Allowable Subject Matter

Claims 96-99 are allowed.

Claims 76, 77, and 83 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form.

Certain papers related to this application may be submitted to Art Unit 1632 by facsimile transmission. The FAX number is (703) 308-4242 or 305-3014. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If applicant *does* submit a paper by FAX, the original copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Scott D. Priebe whose telephone number is (703) 308-7310. The examiner can normally be reached on Monday through Friday from 8 AM to 4 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Karen M. Hauda, can be reached on (703) 305-6608.

Any inquiry concerning administrative, procedural or formal matters relating to this application should be directed to Patent Analyst Patsy Zimmerman whose telephone number is (703) 308-8338. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Scott D. Priebe

Scott D. Priebe, Ph.D.
Primary Examiner
Technology Center 1600
Art Unit 1632